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Variant: NM_000419.5:c.693dup

Version: 1.0

CA915940315

996204 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann's thrombasthenia (MONDO:0010119)
Inheritance Mode: Autosomal recessive inheritance
UUID: 2dce6c82-b717-4714-a586-2af41e85c7d6
Approved on: 2020/12/2
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HGVS expressions

NM_000419.5:c.693dup
NC_000017.11:g.44385055dup
CM000679.2:g.44385055dup
NC_000017.10:g.42462423dup
CM000679.1:g.42462423dup
NC_000017.9:g.39817949dup
NG_008331.1:g.9452dup
ENST00000262407.6:c.693dup
ENST00000648408.1:c.124dup
ENST00000262407.5:c.693dup
ENST00000589645.5:n.144dup
ENST00000591990.5:n.55dup
ENST00000592075.5:n.62dup
ENST00000592226.5:n.39+110dup
ENST00000592253.5:n.201dup
ENST00000592944.1:n.375dup
NM_000419.3:c.693dup
NM_000419.4:c.693dup

Pathogenic

Met criteria codes 4

PVS1 PP4_Strong PM2_Supporting PM3

Evidence Links 0

Expert Panel

Platelet Disorders VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

The ITGA2B frameshift variant NM_000419.5:c.693dup (p.Ala232CysfsTer24) is expected to introduce a premature termination codon 24 amino acids downstream and the resulting mRNA product is predicted to undergo nonsense mediated decay, leading to loss of normal protein function. This variant has been observed in homozygosity in two individuals with a phenotype specific for Glanzmann's thrombasthenia (GT) (GT-9, PMID: 25539746 and Patient ZM, PMID: 12083483). Furthermore, this variant is absent from population

databases. In summary, this variant meets criteria to be classified as pathogenic for GT. GT-specific criteria applied: PVS1, PM3, PP4_strong, PM2_supporting.

Met criteria codes

PVS1	✔	This variant introduces a frameshift in exon 7/30 resulting in a premature termination codon 24 amino acids downstream. The resulting mRNA product is predicted to undergo nonsense mediated decay, leading to loss of normal protein function.
PP4_Strong	✔	This variant was reported in homozygosity in two individuals (GT-9, PMID: 25539746 and Patient ZM, PMID: 12083483). At least one of these individuals (Patient ZM, PMID: 12083483) meets all requirements for PP4 at an upgraded strength of strong (PP4_strong): epistaxis; absent platelet aggregation in response to physiologic agonists except normal response to ristocetin; flow cytometry showed trace expression of αIIb; direct sequencing of all exons and intron/exon boundaries of ITGA2B and ITGB3.
PM2_Supporting	✔	This is a rare variant not reported in control population databases, including gnomAD v2.1.1, gnomAD v3, PAGE, 1000 Genomes, and ESP, meeting the criterion to apply PM2_supporting.
PM3	✔	This variant has been observed in homozygosity in two individuals (GT-9, PMID: 25539746 and Patient ZM, PMID: 12083483), sufficient to apply PM3.

Curation History

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